

Antibiotic Susceptibility Testing: Practical Implications

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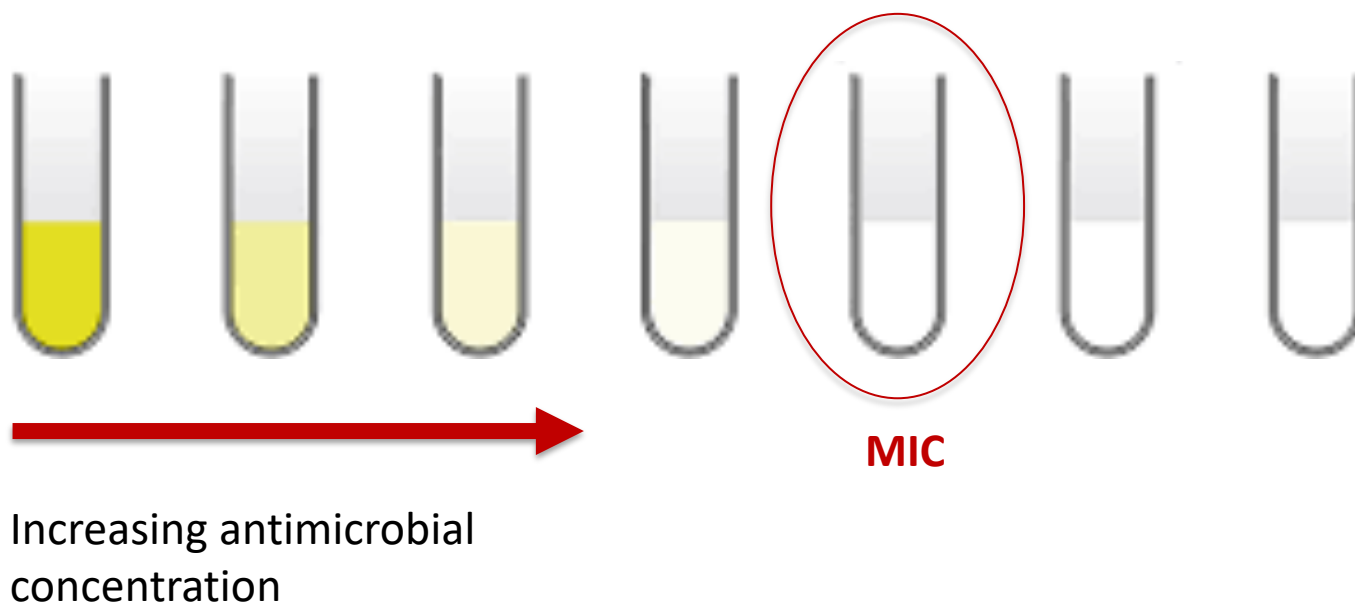
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The Minimum Inhibitory Concentration

Broth Dilution

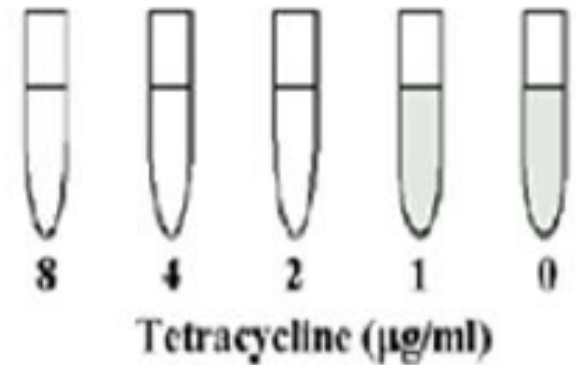
The minimum inhibitory concentration (MIC):

The lowest concentration of a drug which prevents visible bacterial growth



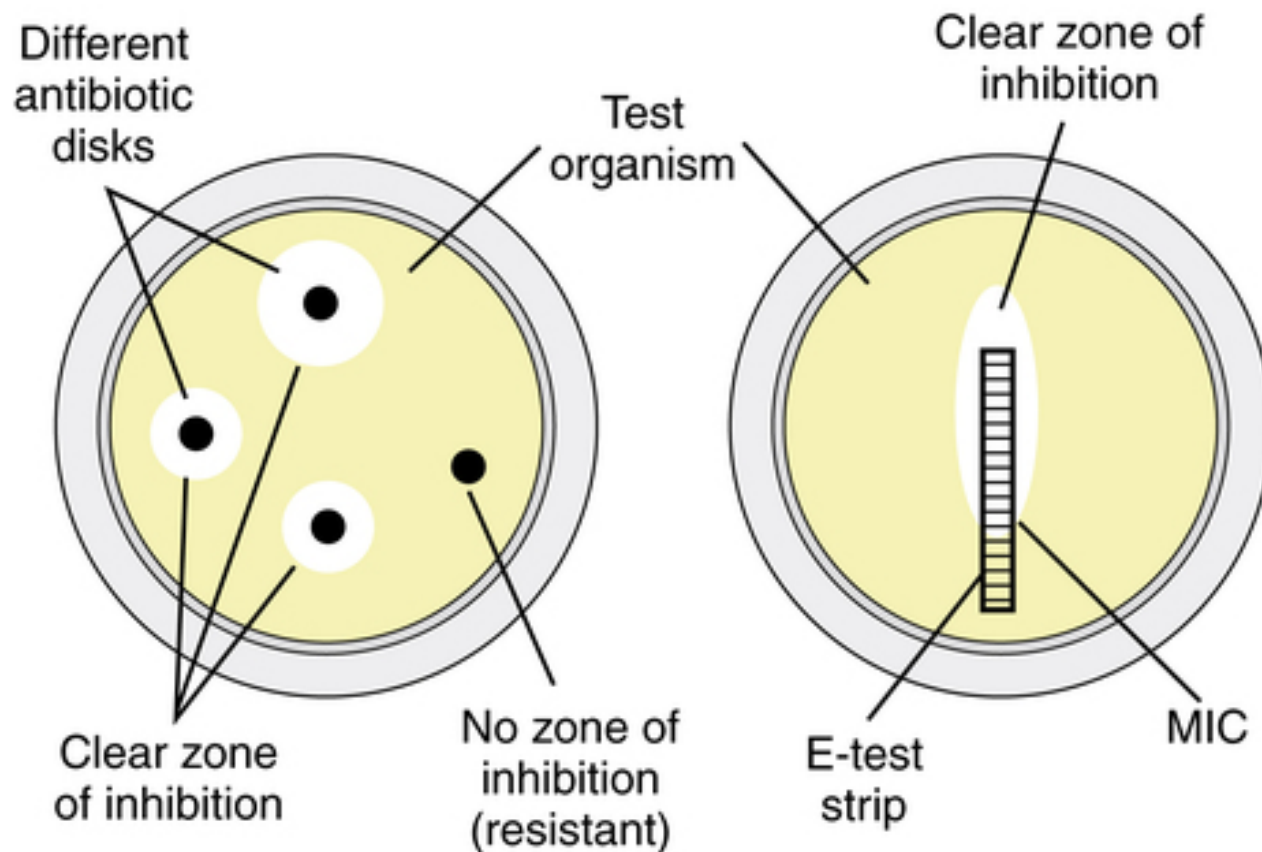
What is the minimum inhibitory concentration in the broth microdilution test?

- A. 8
- B. 4
- C. 2
- D. 1
- E. 0



Other Antibiotic Susceptibility Tests

Disk Diffusion & E-Test



Antimicrobial Breakpoint

Susceptibility

Staphylococcus aureus, Methicillin resistant (MRSA)	
Clindamycin	S
Tetracycline	S
Trimethoprim + Sulfamethoxazole	S
Vancomycin	S

Staphylococcus aureus, Methicillin resistant (MRSA)

Isolated from both bottles of set

This MRSA has an MIC for Vancomycin that is equal to or greater than 1 microgram per milliliter. This has been associated with an increased risk of treatment failure.

POSITIVE for MRSA (methicillin-resistant Staphylococcus aureus) by nucleic acid test in both bottles of set.

Vancomycin MIC by E test 1.0, Sensitive.

How are your hospital's microbiology results reported?

- A. Susceptible/Resistant/Intermediate (S/I/R) ONLY
- B. S/I/R + the numerical MIC (e.g. S, MIC = 2)
- C. Not sure

Susceptibility

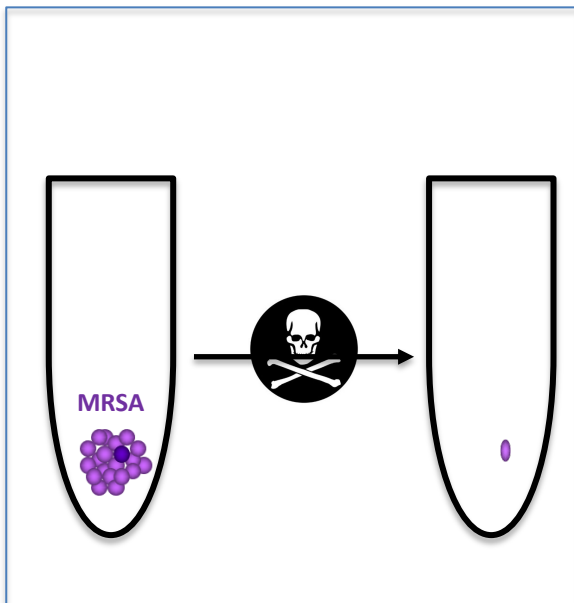
Staphylococcus aureus, Methicillin resistant (MRSA)	
Clindamycin	S
Tetracycline	S
Trimethoprim + Sulfamethoxazole	S
Vancomycin	S

MIC $\neq$ Breakpoint

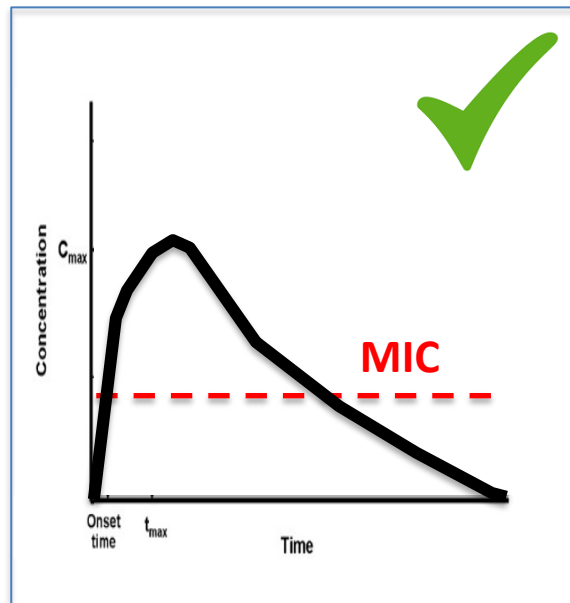
The Breakpoint:

Breakpoint setting integrates knowledge of **wild-type MICs**, assessment of antimicrobial **pharmacokinetics and pharmacodynamics**, and studies of **clinical outcomes** when the antimicrobial is used

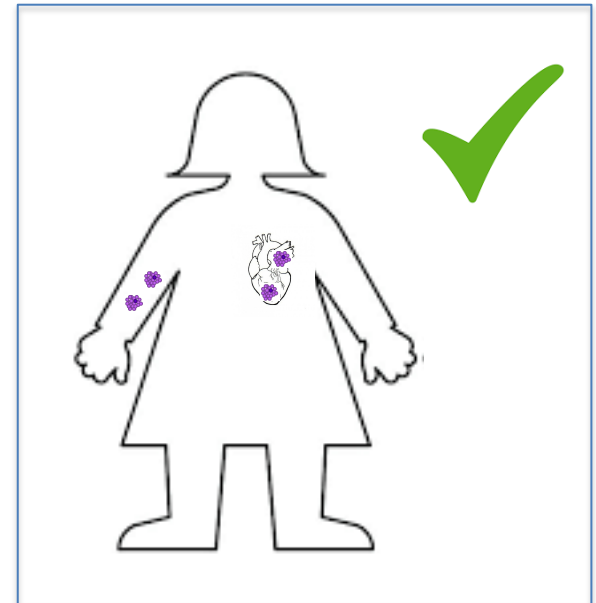
MIC



PK/PD



Clinical Outcomes

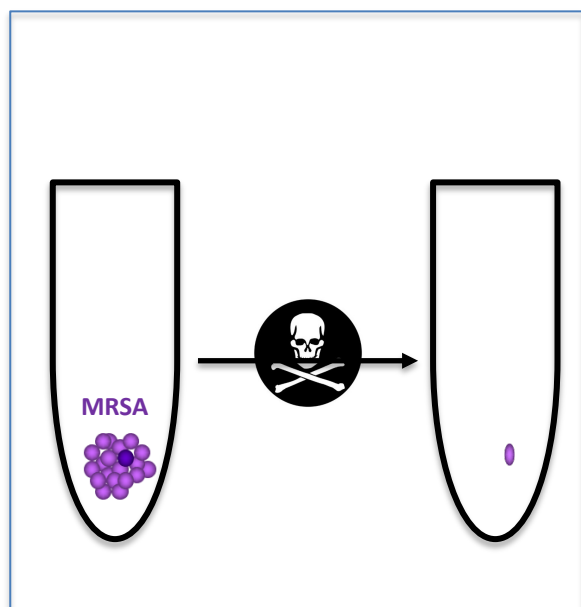


MIC $\neq$ Breakpoint

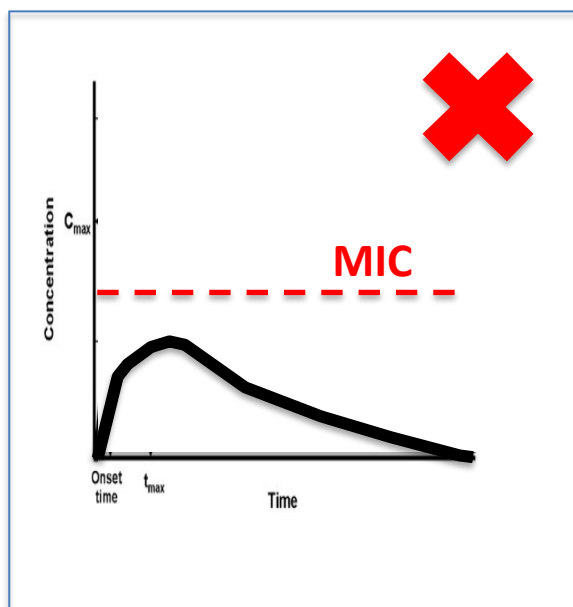
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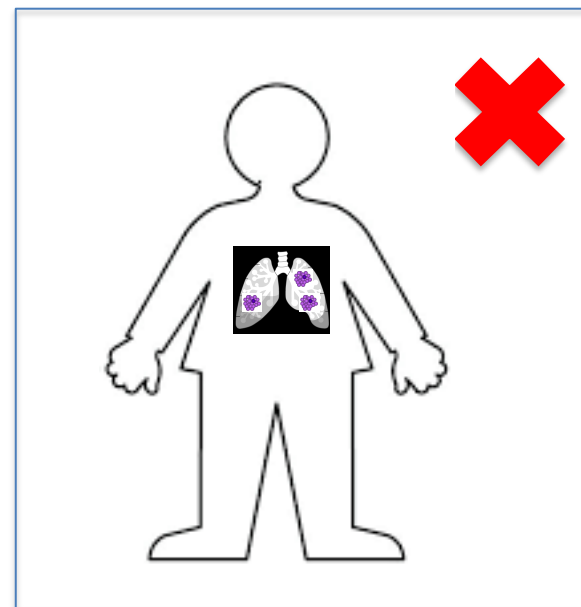
MIC



PK/PD



Clinical Outcomes



A 48 y.o. male presents with
E. coli urosepsis.
 MD asks is it okay to
 de-escalate to cefazolin?

- A. YES, this is a pan-sensitive organism
- B. NO, no cefazolin susceptibility data for blood culture
- C. Not sure/Need more data

RESULTS – BLOOD, VENOUS <i>Escherichia coli</i>	
Antibiotic	Susceptibility
AMP/AMOXICILLIN	S
AMPICILLIN + SULBACTAM	S
AZTREONAM	S
CEFTRIAXONE	S
ERTAPENEM	S
GENTAMICIN	S
LEVOFLOXACIN	S
PIPERACILLIN/TAZOBACTAM	S
TRIMETHOPRIM + SULFAMETHOXAZOLE	S

RESULTS – URINE, CLEAN CATCH <i>Escherichia coli</i> 100,000 CFU	
Antibiotic	Susceptibility
AMP/AMOXICILLIN	S
AMPICILLIN + SULBACTAM	S
AZTREONAM	S
CEFAZOLIN	S
CEFTRIAXONE	S
ERTAPENEM	S
GENTAMICIN	S
LEVOFLOXACIN	S
NITROFURANTOIN	R
PIPERACILLIN/TAZOBACTAM	S
TRIMETHOPRIM + SULFAMETHOXAZOLE	S

MIC Breakpoint

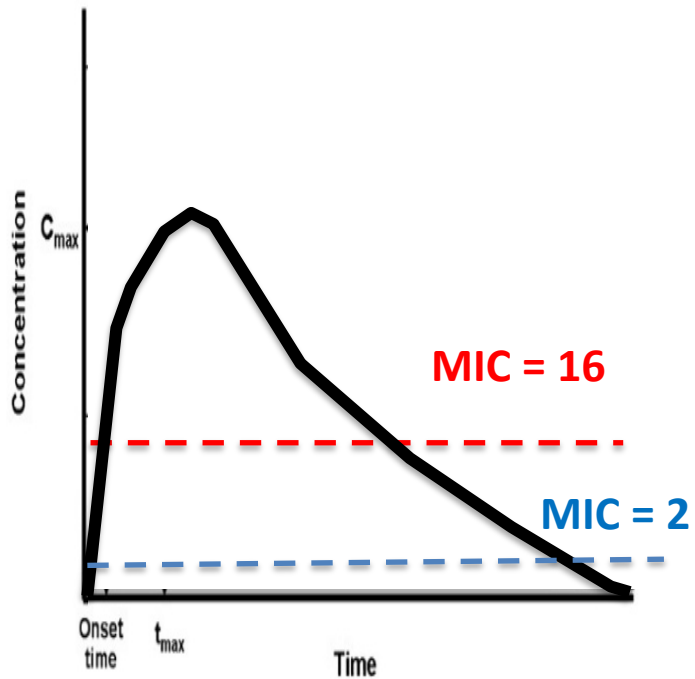
Table 2A. *Enterobacteriaceae* (Continued)

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
A	Cefazolin	30 µg	≥ 23	—	20–22	≤ 19	≤ 2	—	4	≥ 8	(11) Breakpoints when cefazolin is used for therapy of infections other than uncomplicated UTIs due to <i>E. coli</i> , <i>K. pneumoniae</i> , and <i>P. mirabilis</i> . Breakpoints are based on a dosage regimen of 2 g every 8 h. See comment (9).
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.) (Continued)											
U	Cefazolin	30 µg	≥ 15	—	—	≤ 14	≤ 16	—	—	≥ 32	(12) Breakpoints when cefazolin is used for therapy of uncomplicated UTIs due to <i>E. coli</i> , <i>K. pneumoniae</i> , and <i>P. mirabilis</i> . Breakpoints are based on a dosage regimen of 1 g every 12 h. See additional information in CEPHEMS (ORAL).

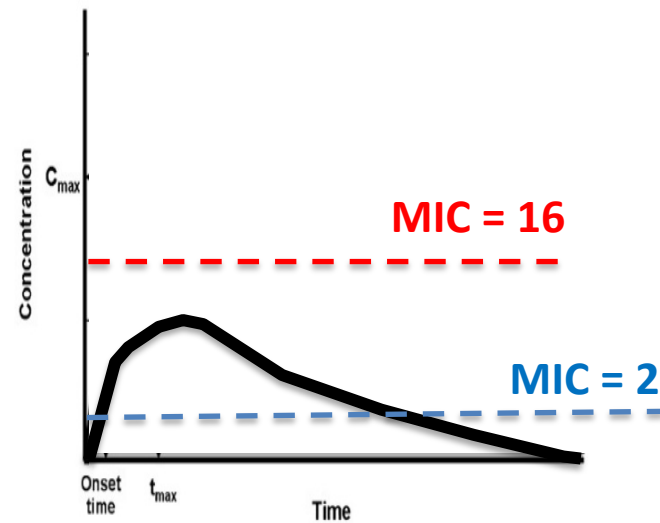
2 different breakpoints for Cefazolin: Uncomplicated UTI vs. All other infections

Why 2 Breakpoints: PK/PD

URINE Concentrations of Cefazolin



BLOOD Concentrations of Cefazolin



A 48 y.o. male presents with *E. coli* urosepsis.

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RESULTS – BLOOD, VENOUS <i>Escherichia coli</i>	
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GENTAMICIN	S
LEVOFLOXACIN	S
PIPERACILLIN/TAZOBACTAM	S
TRIMETHOPRIM + SULFAMETHOXAZOLE	S

RESULTS – URINE, CLEAN CATCH <i>Escherichia coli</i> 100,000 CFU	
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AZTREONAM	S
CEFAZOLIN	S
CEFTRIAXONE	S
ERTAPENEM	S
GENTAMICIN	S
LEVOFLOXACIN	S
NITROFURANTOIN	R
PIPERACILLIN/TAZOBACTAM	S
TRIMETHOPRIM + SULFAMETHOXAZOLE	S

- YES, this is a pan-sensitive organism
- NO, no cefazolin susceptibility data for blood culture
- Not sure/Need more data  **Get a cefazolin disk test**

MIC Breakpoint

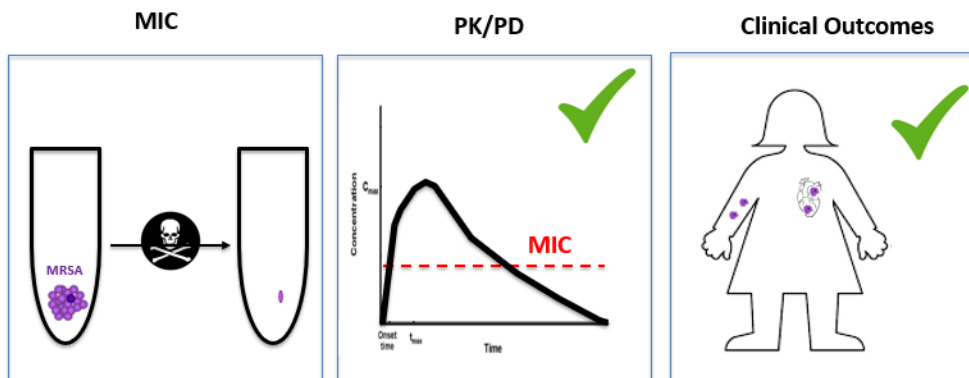
BP* Comments

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*Breakpoint Comments include:

- Dosing regimen for PK/PD rationale
- Site of infection/bacterial organisms for clinical rationale



An 83 y.o. female presents with altered mental status. She is found to have cystitis with VRE*

What is the most appropriate treatment?

- A. PO Amoxicillin
- B. PO Nitrofurantoin
- C. PO Linezolid
- D. IV Daptomycin

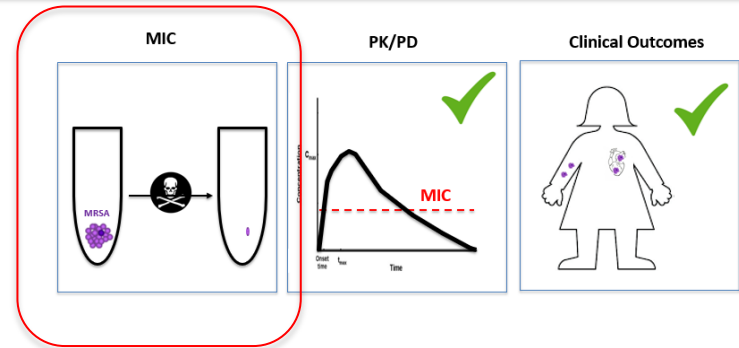
*Vancomycin resistant Enterococcus

RESULTS – URINE, CLEAN CATCH
***Enterococcus Faecium* (VRE)**

Antibiotic	Susceptibility
AMP/AMOXICILLIN	R
NITROFURANTOIN	S
VANCOMYCIN	R
DAPTOMYCIN	S
LINEZOLID	S

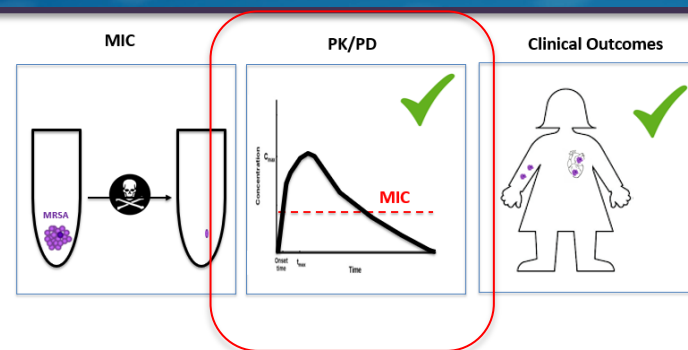
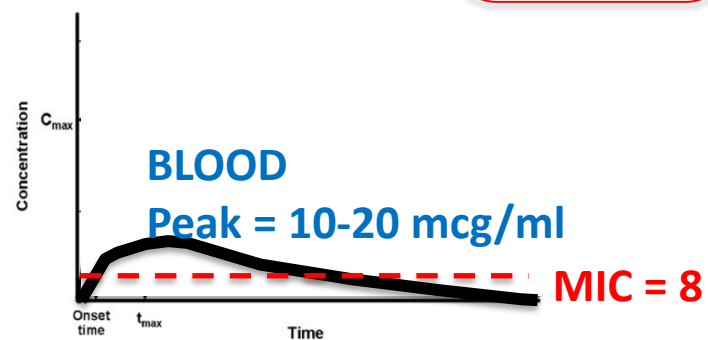
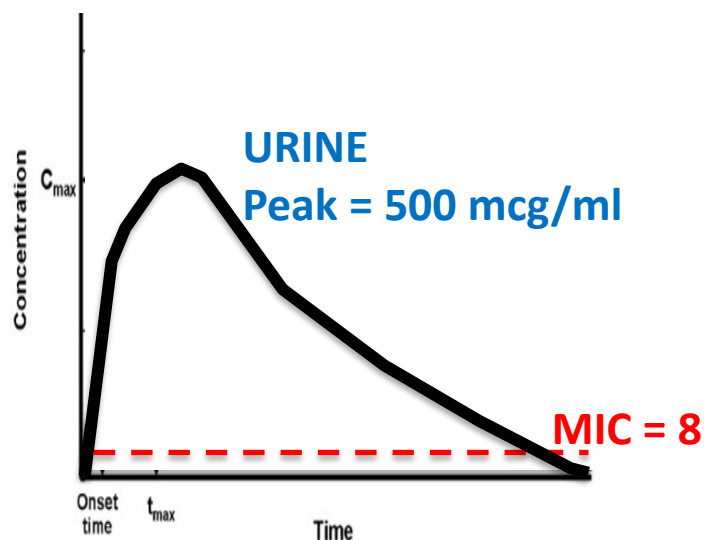
Rationale for Aminopenicillins and VRE

- **MIC Breakpoint: ≤ 8 mcg/ml**



Rationale for Aminopenicillins and VRE

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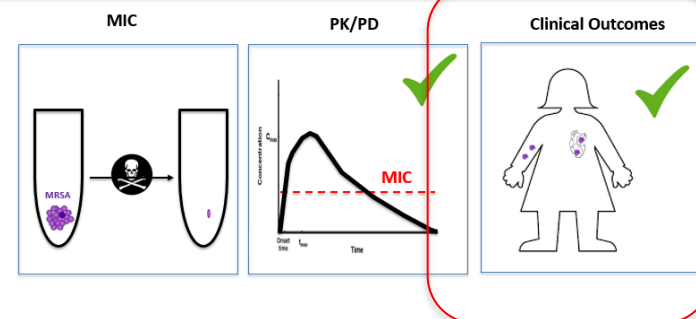
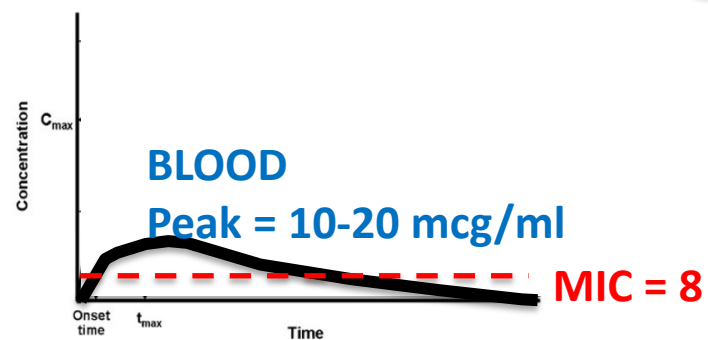
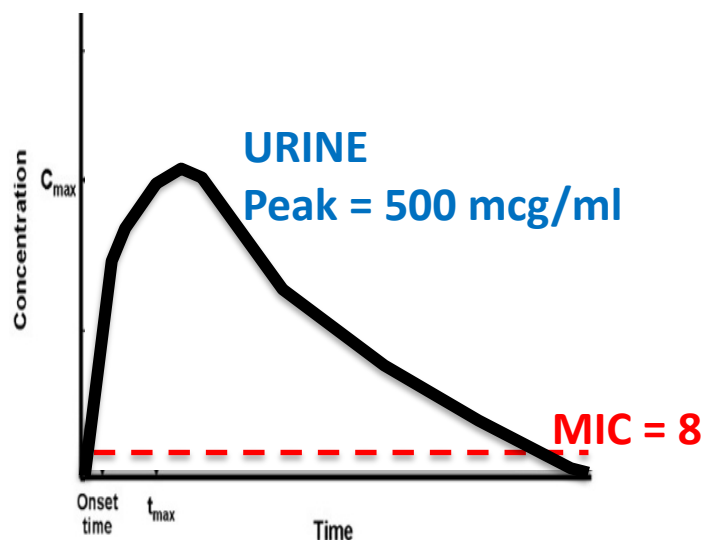


CLSI M100-ED28:2018 Performance Standards for Antimicrobial Susceptibility Testing: 28th Edition.
Antimicrob Agents Chemother 2015;59:7362–7366.

Urine--specific ampicillin breakpoints to improve treatment of Enterococcal urinary tract infections. The Society of Healthcare Epidemiology of America. Orlando FL, May 205. Abstract 6916.

Rationale for Aminopenicillins and VRE

- **MIC Breakpoint: ≤ 8 mcg/ml**
- **PK/PD: Time > MIC**



- **Clinical Data:** Single-center retrospective investigation

	Amp/Amoxicillin	Linezolid/Daptomycin
Clinical Cure	84%	73%
Bacterial Persistence	3.2%	23%

An 83 y.o. female presents with altered mental status
She is found to have cystitis with VRE
(Vancomycin resistant *Enterococcus*)

What is the most appropriate treatment?

- A. **PO Amoxicillin**
- B. PO Nitrofurantoin
- C. PO Linezolid
- D. IV Daptomycin

MIC Varies by Test

Table 2. Distribution of Vancomycin Minimum Inhibitory Concentration (MIC) by Etest and Broth Microdilution Among All Patients (*n* = 532)

Vancomycin MIC Etest, µg/mL	Vancomycin MIC broth microdilution, µg/mL				Total no. (%)
	.25	.5	1	2	
.38	1	0	0	0	1 (.2)
.5	0	2	1	0	3 (.6)
.75	0	8	3	0	11 (2.1)
1	0	26	31	1	58 (10.9)
1.5	0	31	241	5	277 (52.0)
2	0	3	144	12	159 (29.9)
3	0	0	16	7	23 (4.3)
Total no. (%)	1 (.2)	70 (13.1)	436 (82.0)	25 (4.7)	532 (100)

NOTE. Data are expressed as numbers of patients.

Summary & Conclusions

- Antibiotic breakpoints are *DYNAMIC* and are informed by:
 - Drug concentration required to inhibit the organism
 - May vary by testing method
 - Site of infection
 - Specific organism and the Specific antibiotic
 - PK/PD of the antibiotic
 - Clinical data
- The Clinical Laboratory Standards Institute (CLSI) has many excellent and freely available resources